The Course of Response to Focal/grid Photocoagulation for Diabetic Macular Edema

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The Course of Response to Focal/ Grid Photocoagulation for Diabetic Macular Edema

The Diabetic Retinopathy Clinical Research Network

Abstract

Purpose—To determine whether eyes with center involved diabetic macular edema (DME), treated with focal/grid photocoagulation, in which there is a reduction in central subfield thickness (CST) measured with optical coherence tomography (OCT) after 16 weeks, will continue to improve if retreatment is deferred.

Methods—Prospective, multi-center, observational, single group focal/grid photocoagulation study of 122 eyes with center involved DME (OCT CST ≥250μ). At the 16-week visit and continuing every 8 weeks, eyes were assessed for retreatment and additional laser was deferred if the visual acuity letter score improved ≥5 letters or OCT CST decreased ≥10% compared with the visit 16 weeks prior.

Results—Of the 115 eyes that completed the 16-week visit, 54 (47%) had a decrease in CST by ≥10% compared with baseline. Of these, 26 (48%) had a CST ≥250μ at 16 weeks and were evaluable at 32 weeks. Eleven (42%, 95% confidence interval 23% to 63%) of the 26 eyes had a further decrease in CST ≥10% from 16 to 32 weeks without further treatment.

Conclusion—Sixteen weeks following focal/grid laser for DME, in eyes with a definite reduction, but not resolution, of central edema, 23% to 63% will continue to improve without additional treatment.

Keywords

Focal/Grid Photocoagulation; Diabetic Macular Edema; Optical Coherence Tomography

Introduction

Focal/grid photocoagulation (focal/grid) is the standard treatment for diabetic macular edema (DME).[1] Repetitive photocoagulation was the norm in the Early Treatment Diabetic Retinopathy Study (ETDRS) with a median of 3.8 treatments applied over three years of follow-up (Ferris FL, unpublished data). Retreatment was applied at 4 month intervals if clinically

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*The most recently published list of the Diabetic Retinopathy Clinical Research Network investigators and staff can be found at http://www.drcr.net.

An address for reprints will not be provided.

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A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net

Summary Statement:
Some eyes with diabetic macular edema that improve in retinal thickness but have persistent edema 16 weeks following focal/grid photocoagulation will continue to improve without additional treatment.

significant macular edema persisted, one or more treatable lesions were identified, and the investigator believed these lesions were responsible for the edema.[1]

Studies have shown that photocoagulation can result in retinal pigment epithelial atrophy 200–300% larger than the original laser spot size and can cause secondary choroidal neovascular membranes.[2–4] These complications can lead to loss of central vision, paracentral scotomata, and decreased color vision. Consequently, many retinal specialists today tend to treat with lighter, less intense laser burns than originally specified in the ETDRS,[5] although no clinical trials have been done to show improved outcomes with this approach. Other modifications in the treatment procedures originally specified in the ETDRS protocol have been made without clinical trial evidence of their superiority. These include specification that maximal spot size be 50 microns, allowing the use of yellow wavelength as well as green, not requiring blanching of large microaneurysms as long as the subjacent retinal pigment epithelium is lightly blanched, and removing the requirement for fluorescein angiography to guide treatment.[6, 7] A modified ETDRS focal/ grid photocoagulation protocol including all these changes has been adopted as the standard laser technique for DME used in Diabetic Retinopathy Clinical Research Network (DRCR.net) studies. (www.drcr.net)

An important aspect of focal/grid photocoagulation concerns re-treatment guidelines. In the present work, we investigate this topic. There are limited data on the course of visual acuity and central retinal thickness after a single photocoagulation session for DME. In a DRCR.net clinical trial comparing serial injections of intravitreal triamcinolone with serial focal/ grid photocoagulation treatments, eyes with persistent center involved edema were to receive a second photocoagulation session at 3.5– 4 months unless there was substantial improvement defined as at least a 50% decrease in retinal thickening of the central subfield measurement on Optical Coherence Tomography (OCT).([8, 9]) In a DRCR.net study currently comparing various combination therapies to focal/ grid laser alone, eyes are to receive a second photocoagulation session at 4 months whenever a central subfield thickness (CST) ≥ 250 microns and treatable lesions or thickened macular regions without previous grid treatment are present (protocol available at www.drcr.net date accessed, March 2, 2009). As a result, it is unknown what proportion of eyes with lesser degrees of reduction in retinal thickness would have continued to improve and what the time course for further improvement following the initial photocoagulation session might be. Information derived from four DRCR.net studies (N = 478) indicated that 221 eyes (46%) receiving focal/ grid photocoagulation showed at least 10% improvement in central retinal thickness after 3–4 months (DRCR.net, unpublished data). Of these 221 eyes, 154 (70%) still remained ≥ 250 microns in the central subfield despite the 10% improvement in thickness. It is for these eyes that further knowledge of the course of retinal thickening and visual acuity without additional interventions is needed to assess how often continued improvement might occur in the absence of additional treatment.

We performed a study designed to determine the effect of deferral of retreatment in eyes that were improving after initial focal/ grid laser treatment, but still had residual macular edema 16 weeks later. This information might help guide focal/ grid laser re-treatment protocols, and help investigators decide if a randomized clinical trial is justified comparing the current DRCR.net re-treatment regimen versus a regimen of more prolonged observation before retreatment when improvement occurs.

Methods

This prospective, multi-center, single-group intervention study of subjects with center involved DME (OCT mean CST ≥250 microns) was conducted by the DRCR.net at 26 clinical sites throughout the United States. The protocol and HIPAA-compliant informed consent forms were approved by multiple institutional review boards. Each subject gave written informed

consent to participate in the study. The study is listed on www.clinicaltrials.gov, under identifier NCT00442156 and the protocol is available on the DRCR.net website (www.drcr.net) and summarized below.

Study Population

Eligible subjects had to be at least 18 years old with type 1 or type 2 diabetes. Subjects were excluded if they had a history of chronic renal failure requiring dialysis, poor glycemic control in which intensive insulin treatment had been given in the previous 4 months, blood pressure systolic above 180 or diastolic above 110. Study eyes were to have the following: (1) best corrected electronic-ETDRS (E-ETDRS) visual acuity letter score ≥ 24 (Snellen equivalent of 20/320 or better), (2) retinal thickening due to DME involving the center of the macula on clinical exam, (3) retinal thickness in the central subfield measured on a Stratus (Carl Zeiss Meditec, Dublin, CA) OCT ≥ 250 microns, and (4) focal/grid photocoagulation planned as treatment for DME. A study eye was not eligible if (1) it had received treatment for DME in the past 4 months, had received panretinal (scatter) photocoagulation in the prior 4 months or for which treatment was planned in the next 6 months; (2) had a history of major ocular surgery (including cataract extraction, vitrectomy, scleral buckle, any intraocular surgery) within the prior 4 months or anticipated within the subsequent 6 months, or (3) had a history of YAG capsulotomy performed within the previous 2 months. A subject could have only one study eye.

Synopsis of Study Design

Study eyes received focal/grid photocoagulation and were evaluated for change in visual acuity letter score and OCT CST. Follow-up visits with these measurements were performed at 8-week intervals until exiting the study or out to 48 weeks within pre-specified time windows. At the 8-week visit no treatment decisions were made. At week 16, eyes were classified as improved and further laser was deferred if the VA letter score improved by ≥5 letters or OCT CST decreased by ≥10% compared with baseline. For visual acuity a 5 letter score or greater improvement was considered a real change based on the 95% confidence interval for change determined in a study that evaluated the validity and reliability of the E-ETDRS visual acuity testing procedure that is used in DRCR.net protocols.[10] The 10% CST threshold is based on the DRCR.net OCT reproducibility study which found that a 10% or greater change in CST was likely to be real.[11] Eyes that improved at week 16 were evaluated every 8 weeks and considered for further treatment deferral if the visual acuity letter score or OCT CST improved compared to the visit 16 weeks earlier. If eyes did not improve as described above according to the visual acuity letter score or OCT at any visit starting with week 16 and additional laser was given, the subject exited the study. Eyes that did not improve, but for whom laser was deferred (at the investigator's discretion) also were evaluated every 8 weeks until laser was given or through 48 weeks.

Examination Procedures

At baseline, best-corrected visual acuity was measured at 3 meters. A certified visual acuity examiner completed a refraction following DRCR.net specific protocol and visual acuity testing using the ETDRS electronic method .[10] Optical coherence tomography images were obtained through a dilated pupil by a certified operator using the Zeiss Stratus OCT machine (Carl Zeiss Meditec, Dublin, CA) Scans were 6 mm in length and included the 6 radial line fast macular scan pattern for quantitative measures and the cross-hair pattern (6 to 12 o'clock and 9 to 3 o'clock for qualitative assessment of retinal morphologic features). Images with a center point standard deviation ≥10% of the center point mean were sent to the DRCR.net Reading Center at the University of Wisconsin-Madison for grading.

If the automated thickness measurements were judged by the Reading Center to be inaccurate, center point thickness was measured manually, and this value was used to impute a value for the central subfield (based on a correlation of the 2 measures of 0.98 as published previously imputation was used for 9% of scans). [12]

Treatment Protocol

The focal/grid photocoagulation technique was modified from the original ETDRS protocol as described previously and used in prior DRCR.net protocols.[7] Laser photocoagulation burns were less intense (light gray) and were limited to a smaller spot size (50 μ instead of 50 to 200 μ) than in the original ETDRS protocol.[13] Any laser wavelength between green and yellow was allowed. Blanching of microaneurysms was not required as long as a light gray color change was produced in the subjacent retinal pigment epithelium. In general laser photocoagulation was completed in one sitting and involved focal treatment to all leaking microaneurysms and grid treatment to areas of retinal thickening. The use of a fluorescein angiogram to direct treatment was at investigator discretion.

Statistical Methods

A convenience sample size of approximately 110 eyes was selected for this study. A total of 128 subjects were enrolled, of which 6 subjects were excluded from analysis due to an ineligible baseline OCT (CST <250 microns); 2 of these were due to site errors and 4 were a result of manual grading through Reading Center assessment.

The main outcome measure was the proportion of subjects with improvement in OCT-measured CST by 10% or more at the 32-week follow-up visit compared with the value at the 16- week visit. Per protocol, subjects treated at the 24-week visit were discontinued from the study. These subjects were considered failures for the primary outcome of change from 16 to 32 weeks. Changes in visual acuity letter score for subjects meeting the primary outcome are described.

Distributions of improvement were tabulated and 95% confidence intervals were calculated. Subjects who missed the 16, 32, or 48 week visits were excluded from the analysis at that time point. SAS software version 9.1 (SAS, Cary, NC) was used for all analyses.

Results

Between January and June 2007, 26 sites enrolled 122 eligible study eyes with center involved DME. The baseline characteristics are reported in Table 1.

Macular Thickness Outcomes

Of the 122 eligible study eyes, 115 (94%) completed the 16-week visit. Of these, 54 (47%) had a reduction in CST on OCT by at least 10% compared with baseline with 26 having CST < 250 microns at 16 weeks. Since eyes with CST < 250 microns at 16 weeks were unlikely to improve further by a substantial amount, these 26 eyes were not evaluated for further improvement at subsequent visits in this analysis.

Among the remaining 28 eyes (23%) with persistent edema that improved from baseline to 16 weeks, a further reduction in CST by 10% or more was evaluated by comparing the OCT CST at the 32 week visit with the CST at the 16 week visit. Twenty-six of the 28 eyes were evaluable at 32 weeks; 4 of the 26 evaluable eyes were treated at the 24-week visit. These 4 eyes were assumed to be failures. Of the 26 eyes, 11 (42% [95% CI 23–63%]) eyes showed reduction of CST by at least 10% from 16 to 32 weeks (Table 2). Thus, continuing improvement from 16

to 32 weeks was seen in 11 of 115 (10%) eyes overall in this study. Seven (58%) of the 12 eyes evaluated at 32 weeks with baseline OCT CST ≥ 400 microns showed an OCT CST reduction from 16 weeks to 32 weeks, compared with 4 (29%) of 14 eyes with baseline OCT CST < 400 microns. The OCT CST at the 48-week visit was also compared with the thickness at the 32-week visit in the same 11 eyes. One subject missed the 48-week visit and was excluded, resulting in 10 evaluable eyes. In 8 of these 10 eyes CST at 32 weeks was < 250 microns and in the remaining 2 eyes retreatment was carried out in conjunction with the 40 week visit.

Table 3 summarizes the macular thickness and re-treatment course followed after the 16-week visit by the 54 eyes that met the OCT CST improvement criterion and the 16 eyes that met only the visual acuity improvement criterion. The 54 eyes meeting the OCT criterion were classified by whether CST was ≥ or < 250 μ at the 16 week visit. In the group with CST < 250 μ, at the last visit CST was < 250 μ in 19 eyes, ≥ 250 μ in 3 eyes, and 3 eyes had been re-treated with focal/ grid photocoagulation prior to the last visit. In the group with CST ≥ 250 μ at 16 weeks, at the last visit CST was < 250 μ in 12 eyes, ≥ 250 μ in 5 eyes, and 10 eyes had been re214 treated with focal/ grid photocoagulation prior to the last visit. Meeting the visual acuity deferral criterion alone at week 16 did not predict the possibility of deferral of re-treatment through 48 weeks of follow-up. Of 14 such eyes with follow-up, 11 were re-treated prior to the last visit and 2 had CST ≥ 250 μ at the last visit.

Visual Acuity Outcomes

Of the 26 evaluable eyes that improved on OCT from baseline but had persistent edema at 16 weeks, 7(27%) also improved by 5 or more letters (1 line) in E-ETDRS visual acuity at 16 weeks. Of the 11 eyes that further improved in OCT CST from 16 weeks to 32 weeks, 4(36%) improved in visual acuity letter score by at least 5 letters, 6 (55%) remained the same (changed by less than 5 letters), and 1 (9%) worsened by at least 5 letters.

At the 16-week visit, 16 eyes improved in visual acuity but did not improve in OCT CST compared with baseline. At the 32-week visit 1 of the 16 eyes had improved in OCT CST from the 16-week visit and from baseline and 10 of the 16 eyes were treated at 24 or 32 weeks. Of the 54 eyes with ≥ 10% reduction in macular thickening at 16 weeks, 10 (19%) showed ≥ 5 letter loss, whereas 19 (35%) improved by ≥ 5 letters.

Discussion

Focal/ grid photocoagulation has been shown to improve visual acuity outcomes in DME compared with no treatment, and to result in superior 2 year visual and macular thickness outcomes compared with serial injections of intravitreal triamcinolone.[9, 13] It is possible that similar or better outcomes might be achieved with fewer focal/grid treatments if current guidelines for laser re-treatment were revised to observe and defer additional treatment in improving eyes if incomplete resolution of macular edema is observed after initial photocoagulation, a situation applicable to 32% of eyes based on DRCR.net studies. Focal/ grid photocoagulation has potential side effects, including laser scar expansion, paracentral scotomata, elevation of central visual field thresholds, and secondary choroidal neovascularization and subretinal fibrosis.[2–4, 14] Modifications to focal/grid photocoagulation technique have been made already in response to these potential side effects. Although clinical trials have not been performed to determine whether outcomes are equivalent with these modifications, comparison across studies suggests that outcomes with current techniques may be similar to those obtained with the original ETDRS technique. Re-treatment guidelines are worthy of attention, because costs of time and money might be lessened if the benefits of focal/ grid photocoagulation in DME could be obtained with fewer treatment sessions.

The results of this prospective, multicenter study suggest that using current treatment protocols, 23% of eyes may show improvement in macular thickness over 16 weeks without fully resolving. In this subset of eyes, continued OCT improvement over the ensuing 16 weeks (from 16 to 32 weeks) occurs in 42% [95% CI 23–63%]. Thus, continuing improvement past 16 weeks is seen in 10% of eyes overall based on this study. Eyes with greater macular thickening had a higher frequency of continued improvement after 16 weeks. We also found that the criterion for re-treatment deferral based on visual acuity improvement alone proved to be poorly predictive for subsequent deferral of re-treatment through 48 weeks of follow-up. Eleven of 16 such eyes (69%) required re-treatment after the 16 week visit.

The precision of our results is limited by the small number of eyes studied, and the results do not imply that visual acuity outcomes will be better if re-treatment is deferred at 16 weeks in such eyes. It is possible that additional improvement might have occurred if treatment had not been withheld at 16 weeks. A randomized clinical trial would be needed to assess whether deferring additional treatment for improving eyes with persistent DME is of greater benefit compared with retreating all eyes with center involved edema.

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Executive Committee: Neil M. Bressler (Chair 2006 - present), Lloyd Paul Aiello (2002-present; Chair 2002 – 2005), Andrew N. Antoszyk (2009), Roy W. Beck (2002-present), Susan B. Bressler (2009- Present), Alexander J. Brucker (2009-present), Ronald P. Danis (2004-present), Matthew D. Davis (2002- present), Michael J. Elman (2006-present), Donald F. Everett (2002-present), Frederick L. Ferris(2002- present), Joan Fish (2008 - present), Scott Friedman (2007 –present), Adam R. Glassman (2002-present) Joseph Googe (2009-present), Raj K. Maturi (2009-present), Ingrid U. Scott (2009-Present). Prior Members: Abdhish Bhavsar (2007–2008), David M. Brown (2006–2007), David J. Browning (2005–2006), Andreas Lauer (2007–2008) Kim McLeod (2002–2006), Päivi H. Miskala(2005–2007), Cynthia J. Grinnell (2006–2007).

Table 1

Baseline Characteristics

	Total N=122
Gender: Women – n *(%)*	60 (49%)
Age (yrs) - *Median (25^{th}, 75^{th} percentile)*	65 (57, 72)
Race- n*(%)*	
White	86 (70%)
African-American	18 (15%)
Hispanic or Latino	12 (10%)
Asian	2 (2%)
Other*	4 (3%)
Diabetes Type - n*(%)*	
Type 1	7 (6%)
Type 2	115 (94%)
Duration of Diabetes (years) - *Median (25^{th}, 75^{th} percentile)*	19 (12, 24)
HbA1c (%) - *Median (25^{th}, 75^{th} percentile)* †	7.4 (6.6, 8.5)
Prior treatment for DME in study eye – *n (%)*	58 (48%)
May have had more than one type of treatment	
Focal/grid laser photocoagulation- *n (%)*	55 (45%)
Intravitreal Corticosteroids- *n (%)*	18 (15%)
Peribulbar Corticosteroids - *n (%)*	2 (2%)
Anti-VEGF- *n (%)*	3 (2%)
Prior Panretinal Photocoagulation in study eye – *n (%)*	24 (20%)
E-ETDRS Visual Acuity (letter score)- *Median (25^{th}, 75^{th} percentile)*	72 (62, 79)‡
Central Subfield Thickness (microns)- *Median (25^{th}, 75^{th} percentile)*	330 (279, 402)
Retinal Volume (*mm*^{3})-*Median (25^{th}, 75^{th} percentile)*§	7.9 (7.4, 8.8)

*Other race category includes: American Indian/Alaskan Native, more than one race, and unknown.

†3 subjects missing baseline HbA1c

‡Snellen equivalent=20/40 (20/63,20/25)

§4 subjects missing baseline retinal volume

Table 2

Evaluation of OCT Improvement

	N
Total # Enrolled	N=128
# ineligible	6
# treated prior to 16 week visit	1
# dropped/missed prior to 16 week visit	6
# eligible completing 16 week visit	115
At 16-week visit	N=115
OCT CSF improved from baseline by ≥10%- *N*(%)	54(47%)
OCT CSF < 250 μ- N (exited subsequent analyses)	26
OCT CSF ≥ 250 μ -N	28
Improved from baseline and OCT CSF ≥ 250 μ at 16 weeks	N=28
# Treated prior to 32 week visit	4
# Dropped/Missed prior to 32 week visit	2
# Completed 32-week Visit	22
At 32-week visit (includes treated at 24 weeks)	N=26
OCT CSF improved from 16-week visit by >10% - *N*(%)	11(42%)
OCT CSF < 250 μ -N	8
OCT CSF ≥ 250 μ -N	3*

* 2 subjects were treated at 40 week visit, 1 subject missed 48 week visit

Table 3

Course Followed Subsequent to Week 16 Visit

Status at week 16		No.	OCT CSF <250 microns at all subsequent visits	OCT CSF ≥250 microns at some visits after 16 weeks and not treated (# < 250 at last visit)	Treated	No visits after 16 weeks
OCT CSF decreased by ≥10% N= 54	and <250 microns	26	18	4(1)	3	1
	and ≥250 microns	28	4	13(8)	10	1
VA improved by ≥5 letters and OCT CSF not decreased by ≥10%		16	0	3(1)	11	2